# Targeted Treatments for Autism: from Genes to Pharmacology

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Yale University School of Medicine

Vice President for Clinical Development,
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# Financial disclosure

Full-time employee, Seaside Therapeutics, Inc.

# Learning objectives

1. Explain the "targeted treatment" approach to drug development for neurodevelopmental disorders
2. Identify the synapse as a convergence point for multiple genetic disorders associated with autism and ID
3. Describe the challenges to demonstrating treatment efficacy on the core symptoms of autism

# Q: Where do pediatric psychopharm drugs come from?

A. Lab research

B. Chance observation

C. Adult drugs


D. The stork

# A: Mostly from adult drugs

A. Lab research – none

B. Chance observation

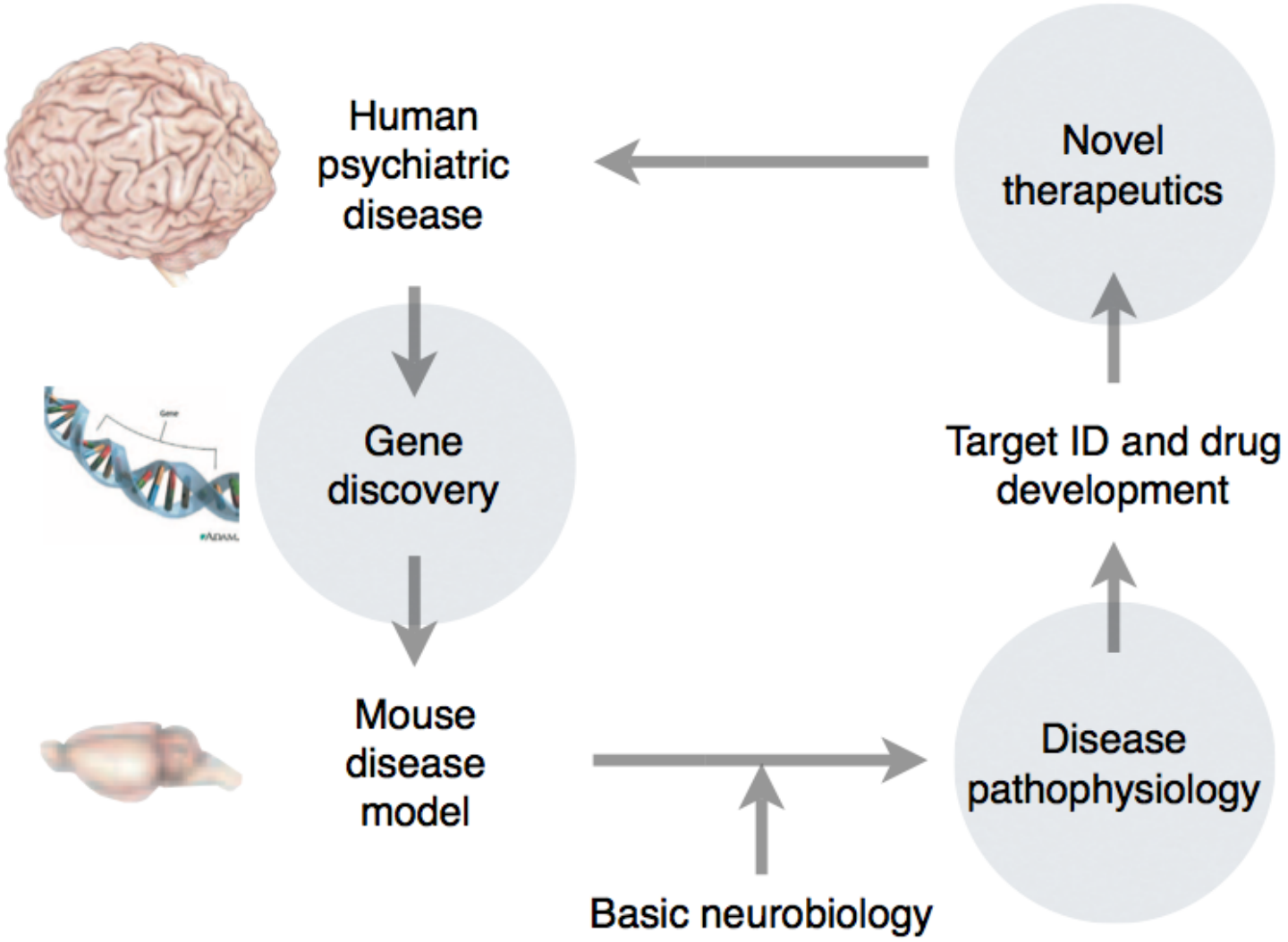
Psychostimulants

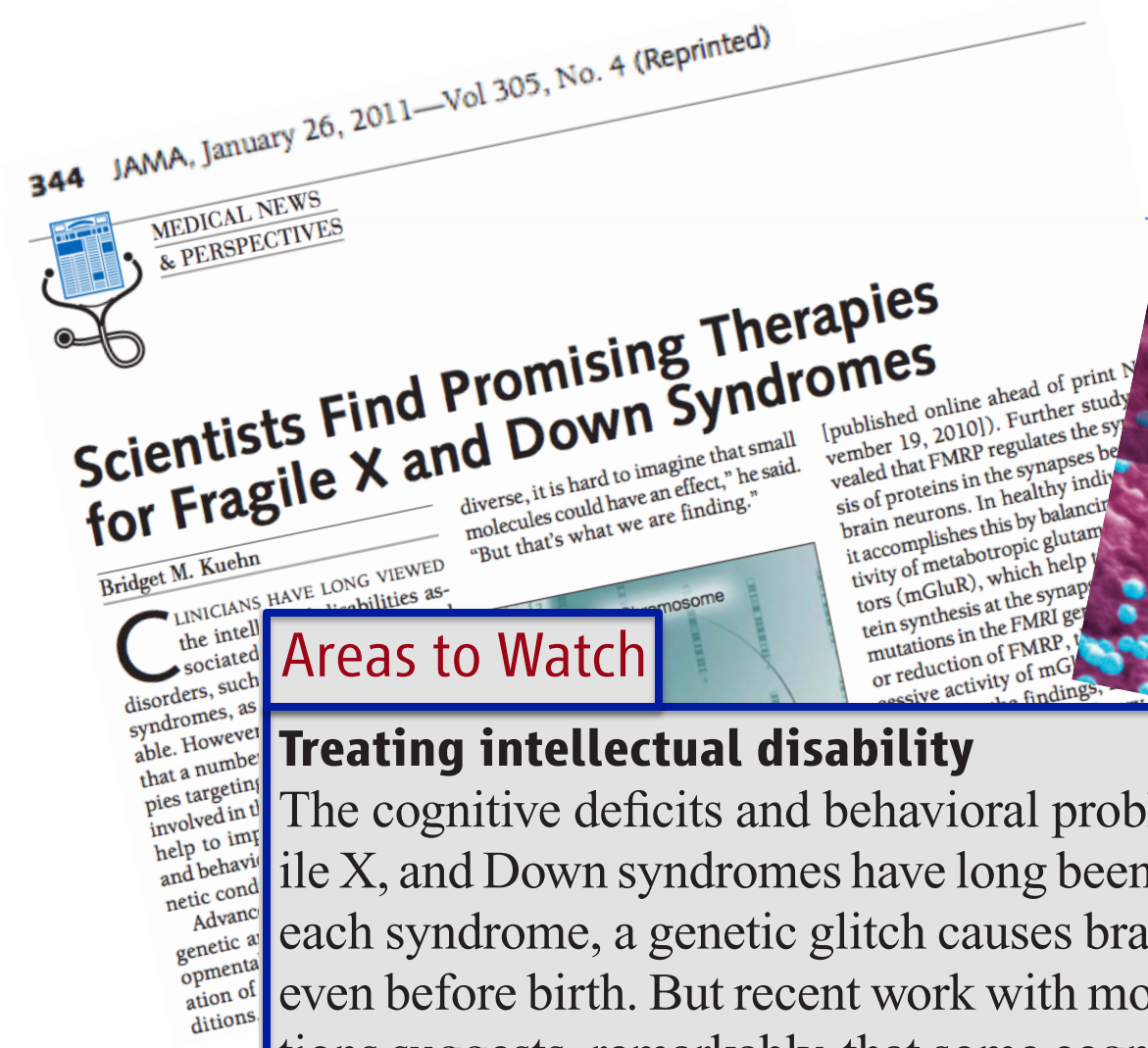
C. Adult drugs

Antipsychotics, anxiolytics, antidepressants, α-adrenergics, atomoxetine, mood stabilizers, antipsychotics for ASD


D. The stork

# A new paradigm for psychopharm drug development





344 JAMA, January 26, 2011—Vol 305, No. 4 (Reprinted)

MEDICAL NEWS & PERSPECTIVES

# Scientists Find Promising Therapies for Fragile X and Down Syndromes

Bridget M. Kuehn

CLINICIANS HAVE LONG VIEWED the intell… sociated… disorders, such… syndromes, as… able. However… that a number… pies targeting… involved in t… help to imp… and behavio… netic cond… Advanc… genetic a… opmenta… ation of… ditions.

diverse, it is hard to imagine that small molecules could have an effect," he said. "But that's what we are finding."

[published online ahead of print N… vember 19, 2010]). Further study… vealed that FMRP regulates the sy… sis of proteins in the synapses be… brain neurons. In healthy indiv… it accomplishes this by balancin… tivity of metabotropic glutam… tors (mGluR), which help t… tein synthesis at the synap… mutations in the FMRI ge… or reduction of FMRP, … essive activity of mG… findings,…


## Areas to Watch

### Treating intellectual disability

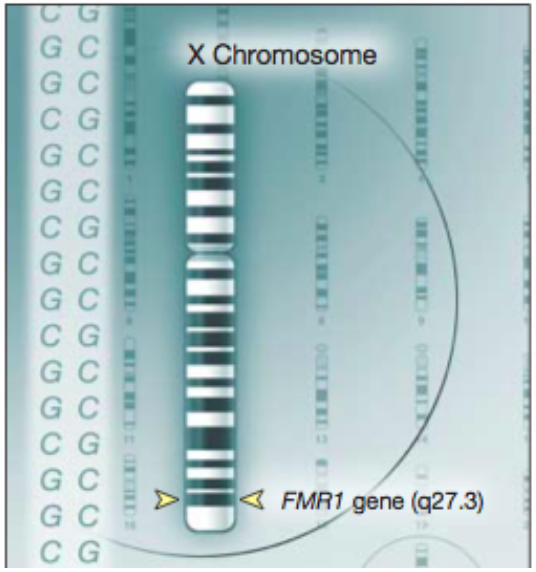
The cognitive deficits and behavioral problems caused by Rett, Fragile X, and Down syndromes have long been considered irreversible. In each syndrome, a genetic glitch causes brain development to go awry even before birth. But recent work with mouse models of these conditions suggests, remarkably, that some cognitive and behavioral symptoms may be reversible. Treatments that target growth factors or neurotransmitter receptors in the brain are now in human clinical trials, and preliminary results should start to emerge in 2012. Meanwhile, expect preclinical researchers to keep coming up with new targets.

# Scientists Find Promising Therapies for Fragile X and Down Syndromes

Bridget M. Kuehn

CLINICIANS HAVE LONG VIEWED the intellectual disabilities associated with developmental disorders, such as fragile X and Down syndromes, as irreversible or untreatable. However, emerging data suggest that a number of potential drug therapies targeting the molecular pathways involved in these disorders may one day help to improve cognition, memory, and behavior in patients with these genetic conditions.

Advances in the understanding of the genetic and molecular basis of developmental disorders, as well as the creation of mouse models for these conditions, have led scientists studying diverse, it is hard to imagine that small molecules could have an effect," he said. "But that's what we are finding."

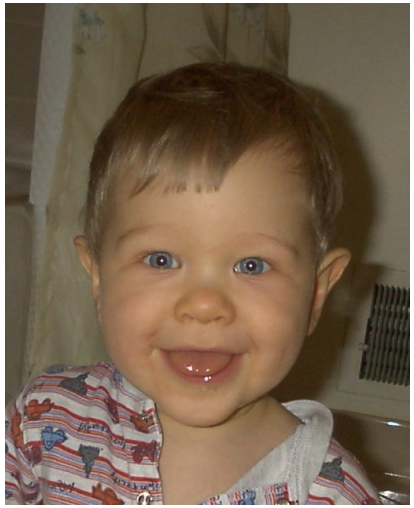



[published online ahead of print November 19, 2010]). Further study revealed that FMRP regulates the synthesis of proteins in the synapses between brain neurons. In healthy individuals, it accomplishes this by balancing the activity of metabotropic glutamate receptors (mGluR), which help trigger protein synthesis at the synapse. But when mutations in the *FMRI* gene cause a loss or reduction of FMRP, the result is excessive activity of mGluR5.

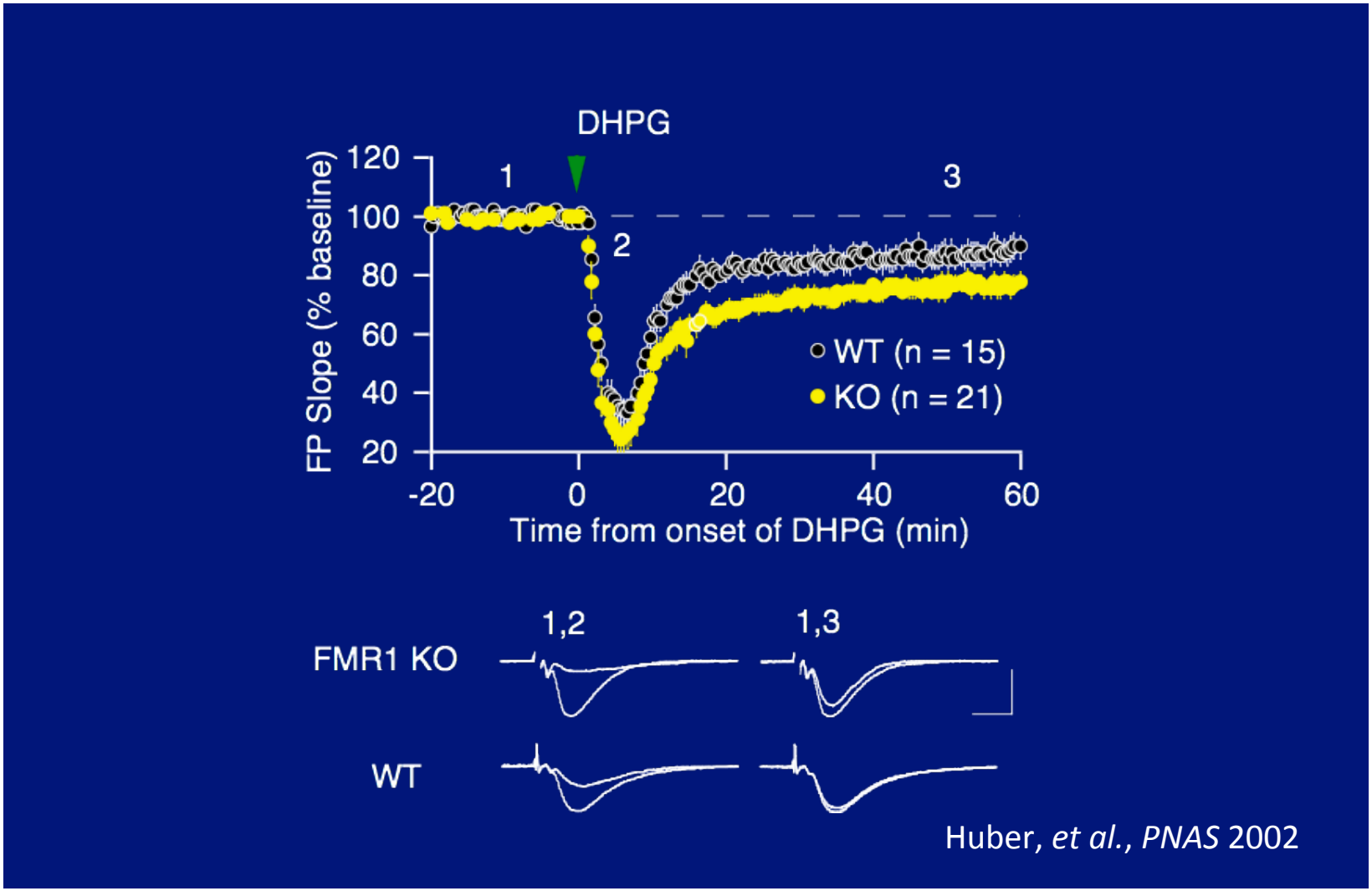
Based on the findings, Bear and his colleagues developed a theory that dysregulation of mGluR signaling caused the neurological deficits seen in the disorder (Bear MF et al. *Trends Neurosci.* 2004;27[7]:370-377). Robert Riddle, PhD, program director of the neuroge-

# Fragile X Syndrome – Clinical overview

- ~ 1:4000 births
- >200 CGG triplet repeats in 5'UTR *FMR1* gene
- Dx by PCR, Southern
- Autistic behaviors, social anxiety
- Moderate to severe intellectual disability (males)
- Seizures, tics, chronic otitis, mitral valve prolapse

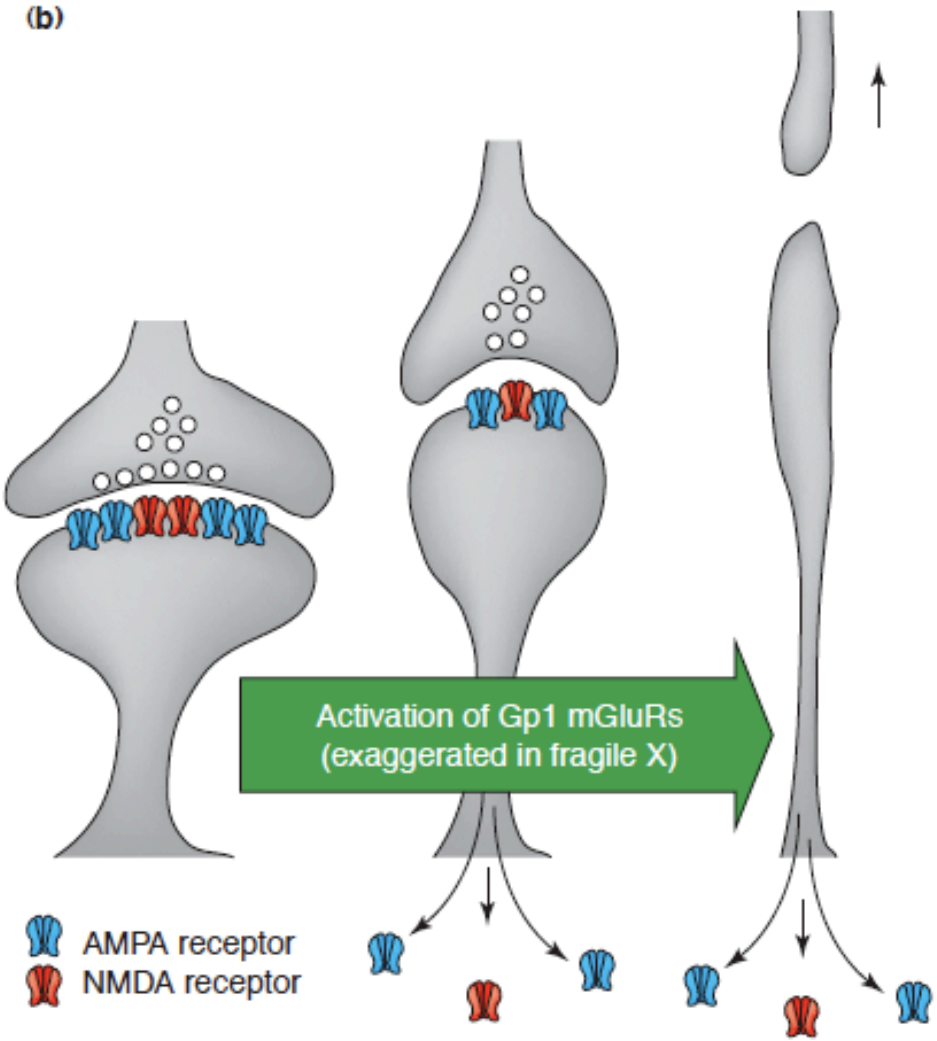


# Abnormal mGluR5-dependent synaptic plasticity in *FMR1* KO mice



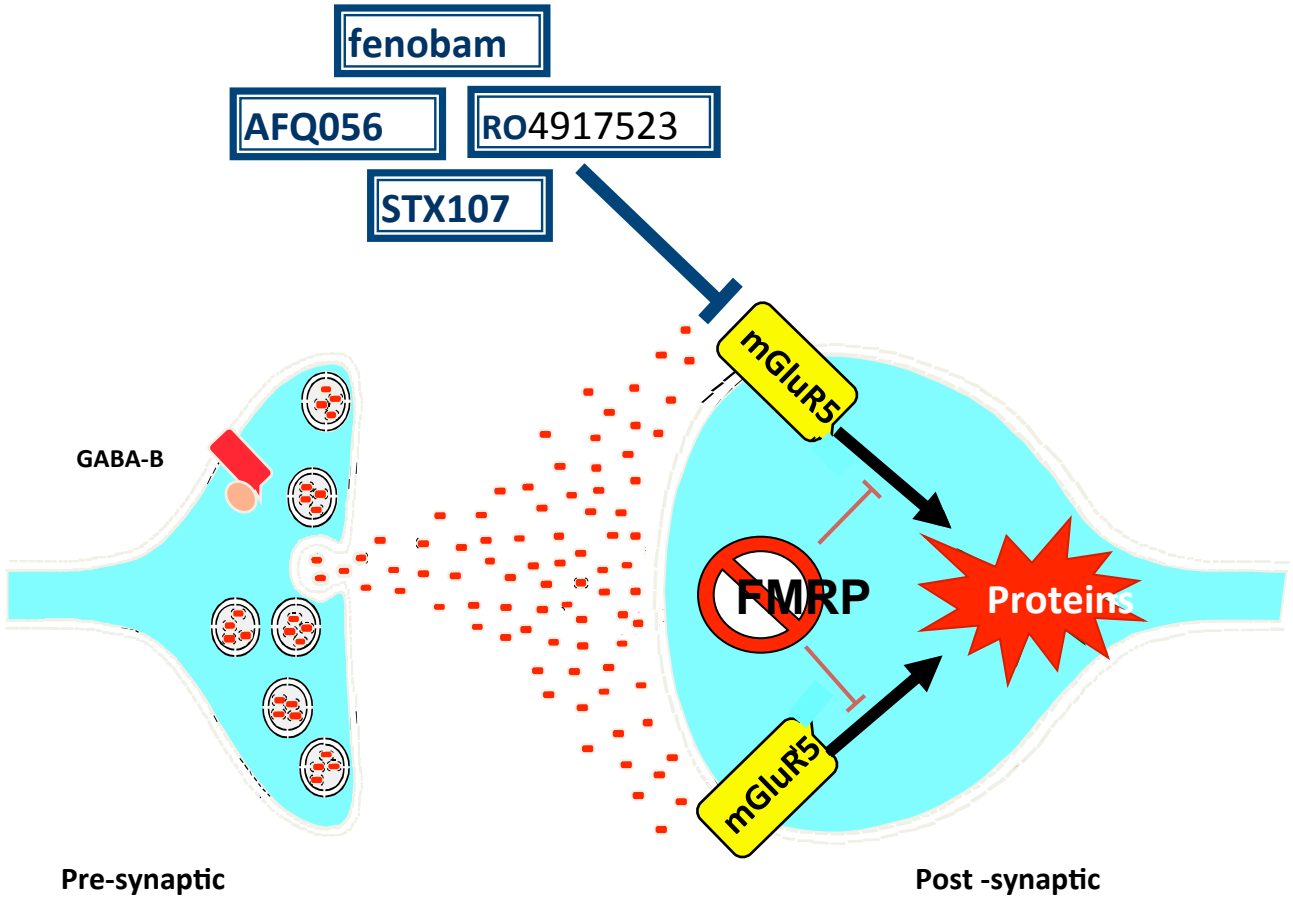

Huber, *et al.*, *PNAS* 2002

# Abnormal synaptic plasticity in *FMR1* KO mice

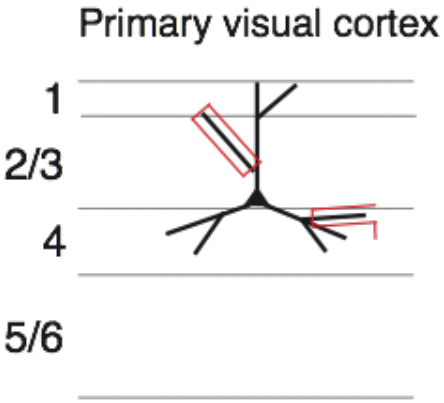


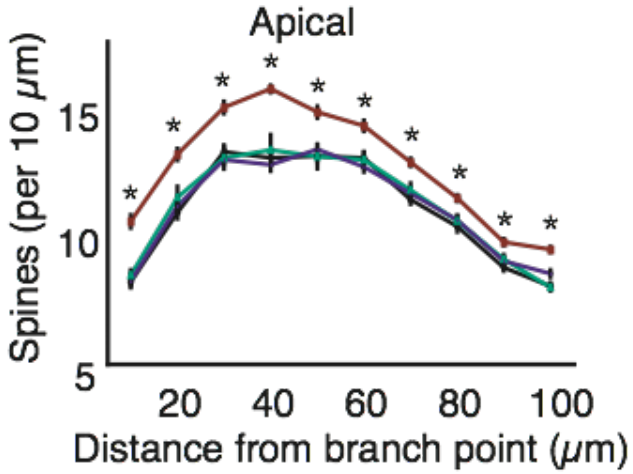

Bear et al., 2004

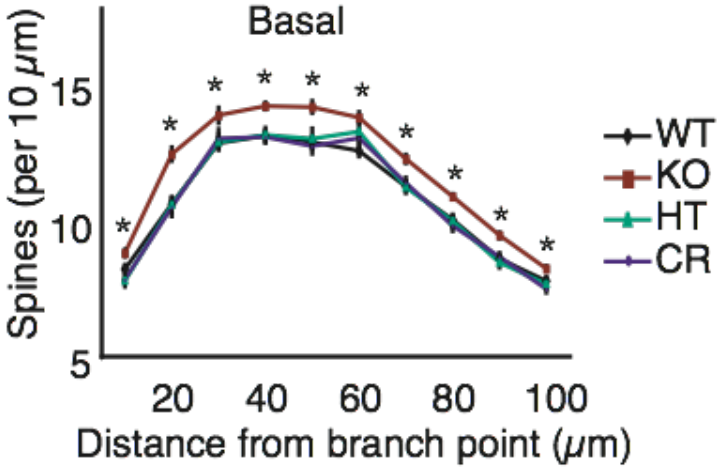
# A therapeutic approach for FXS

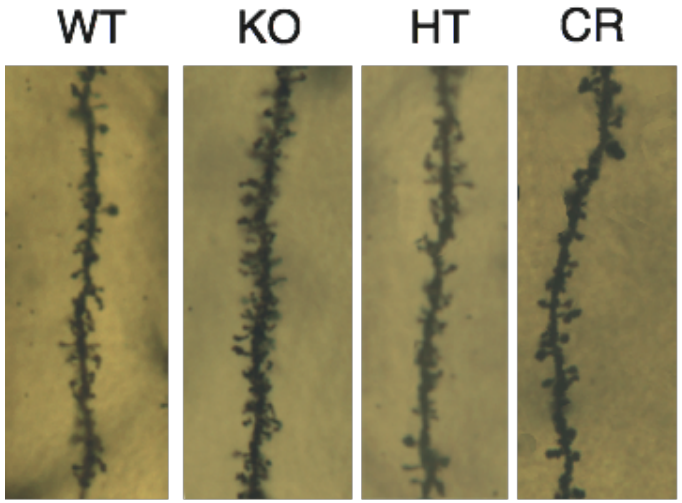


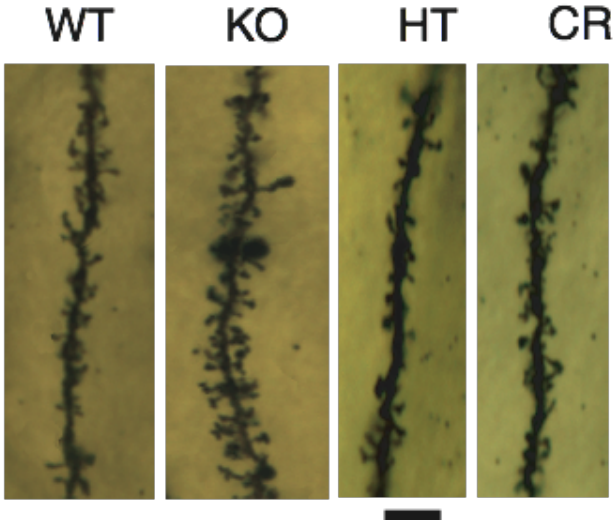
# Rescue of dendritic spine phenotype by mGluR5 knockdown



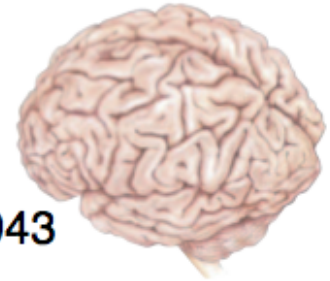



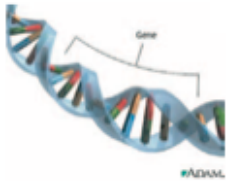



# A new paradigm for psychopharm drug development in fragile X syndrome



1943

Martin-Bell (fragile X) syndrome



1991

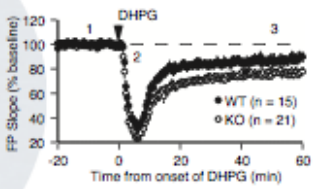
*FMR1* gene silenced by CGG repeat

1994

*Fmr1* knockout mouse

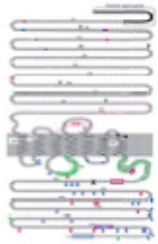
Basic neurobiology

Excessive mGluR5 function



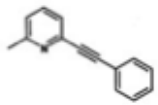

2002

Rescue of *Fmr1* KO by reducing mGluR5

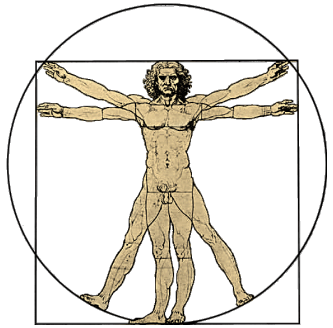


2007

mGluR5 NAMs in phase 2 clinical trails



2010



| FX phenotype | Mouse rescue | | Clinical trial endpoint | FDA approv-able? |
|---|---|---|---|---|
| | mGluR5 | GABA-B | | |
| Increased dendritic spine density | ✔ | ✔ | no | no |
| Increased protein synthesis | ✔ | ✔ | ? | no |
| Increased AMPAR turnover | ✔ | ✔ | no | no |
| Increased marble burying | ✔ | ✔ | no | no |
| Seizure susceptibility | ✔ | ✔ | yes; not needed | possibly |

# Known approvable endpoints for ASD / FXS

- ABC-Irritability subscale (ABC-Irr)
  - with corroborating evidence on CGI
  - must be pre-specified as primary endpoint for study

(none other)

# Open questions in clinical trial design for FXS

- Endpoint
  - Symptom domain
  - Assessment tool
- Effect size / sample size
- Posology
  - Dose
  - Dosing schedule
- Duration of treatment
  - Duration x Dose x Age
- Subject selection
  - Age
  - Symptom severity
  - Co-morbidity
  - Concomitant medications

# Novartis P2 study of AFQ056 in FXS

- Adults with FXS full mutation, n=30
- DB, PC, XO trial – 4 week treatment periods

| | Drug – placebo (90% CI) | p |
|---|---|---|
| Aberrant Behavior Checklist | −2.10 (−8.26 to 4.06) | 0.573 |
| Clinician Global Impression-Imprvmt | 0.01 (−0.38 to 0.41) | 0.955 |
| Vineland Adaptive Behavior Scale | 0.82 (−5.07 to 6.72) | 0.814 |
| Repetitive Behavior Scale-Revised | −3.81 (−6.91 to −0.70) | 0.046 |
| Social Responsiveness Scale | −1.14 (−7.71 to 5.43) | 0.773 |
| Visual Analog Scale | 5.18 (−3.89 to 14.25) | 0.345 |



Jacquemont al., 2011

# AFQ056 effects: Full vs. partial methylation subgroups

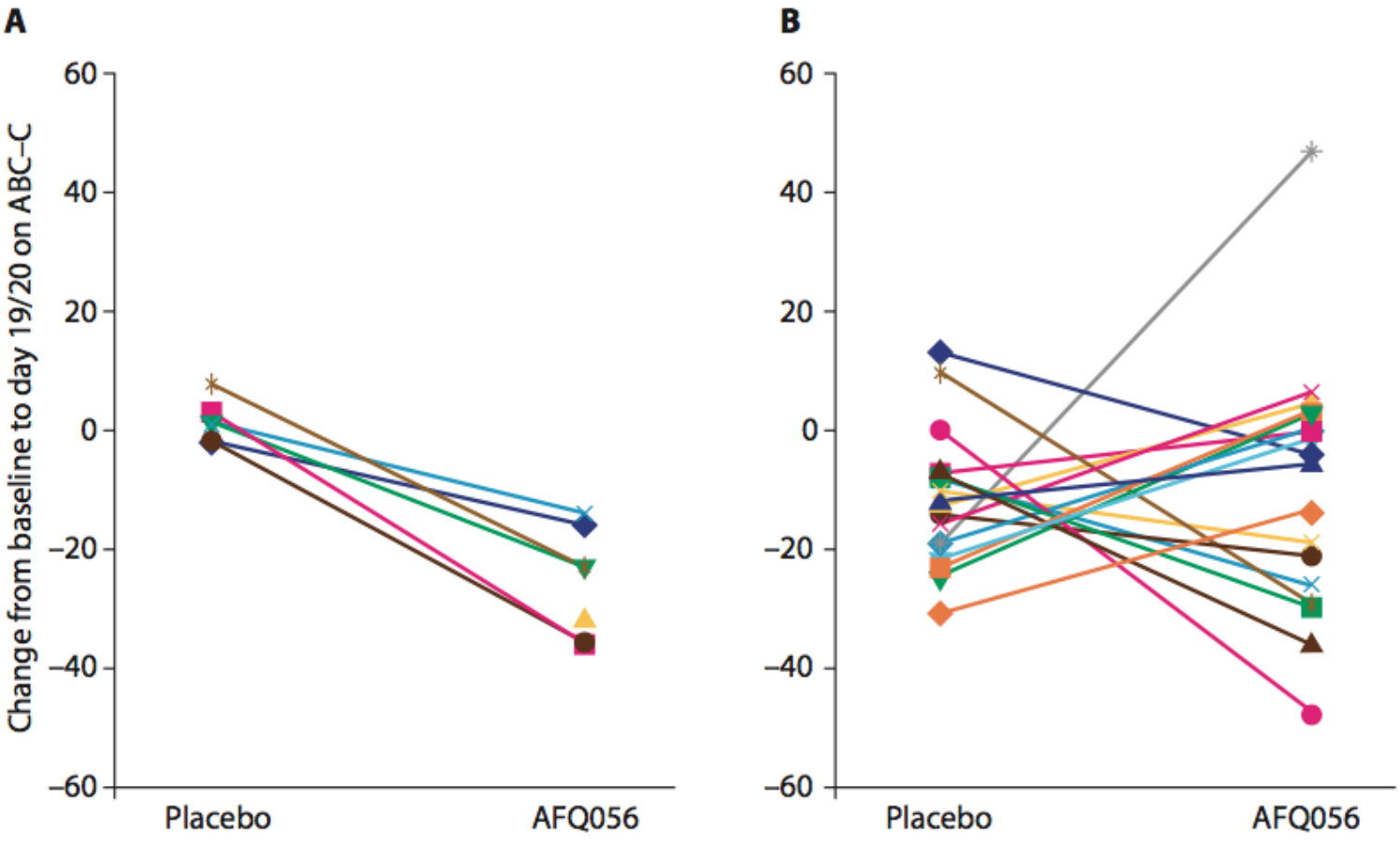
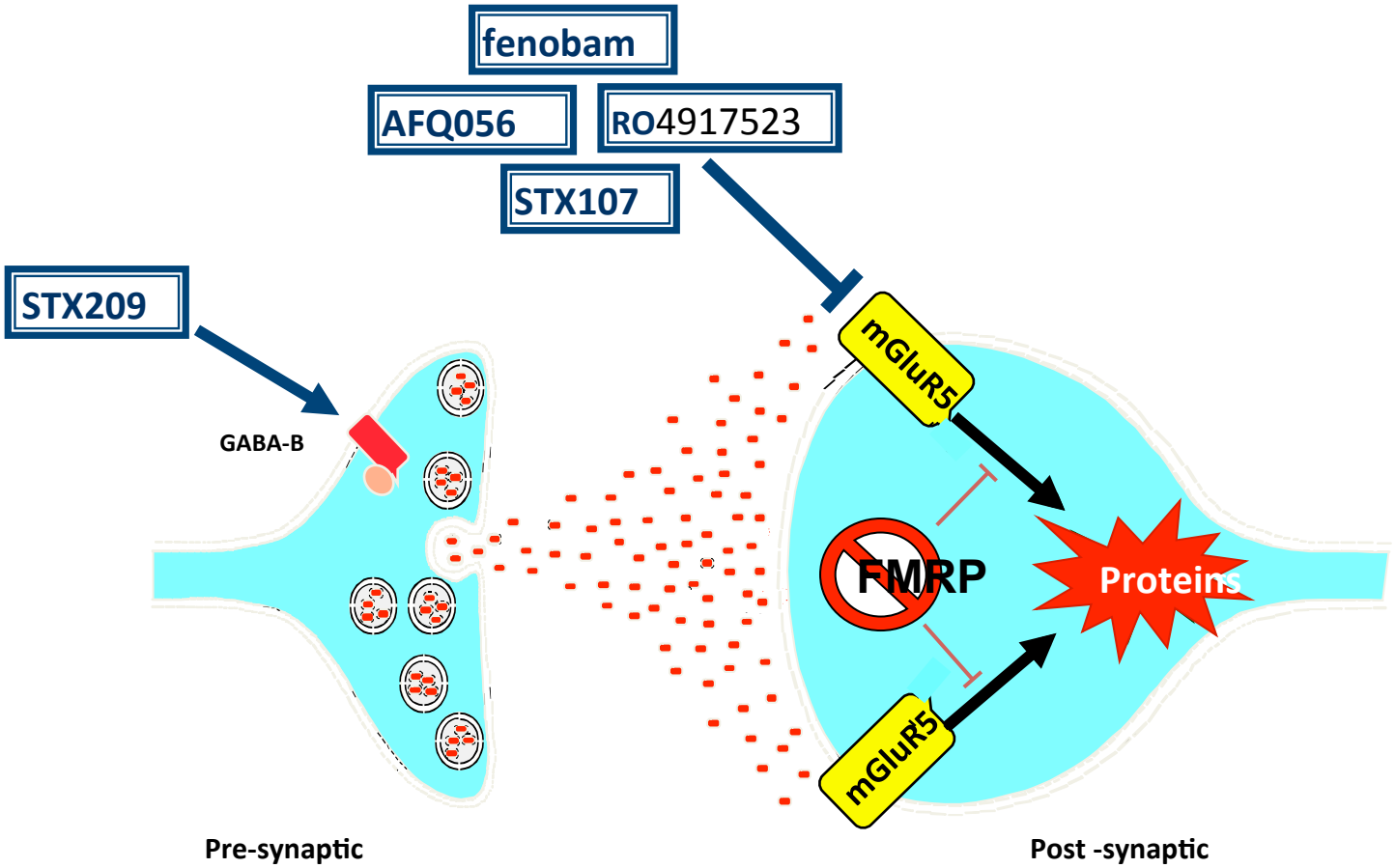



**Fig. 3.** (**A** and **B**) A comparison of the effect of AFQ056 and placebo treatments on the change from baseline to day 19 or 20 on the ABC-C score in individual patients with (A) full methylation at the *FMR1* promoter and (B) partial methylation at the *FMR1* promoter. A decrease in ABC-C score indicates an improvement in behavioral symptoms.

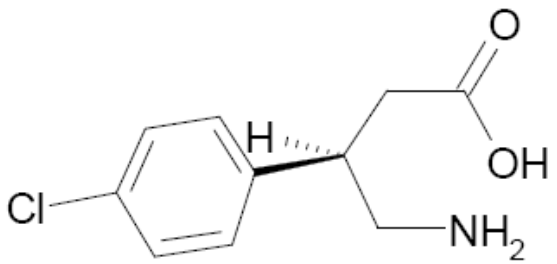
Jacquemont al., 2011

# An alternative therapeutic approach for FXS ?



# STX209 (arbaclofen, R-baclofen)

- Active isomer of racemic baclofen
  - Selective GABA-B agonist
  - R:S isomer potency 10-100:1
  - PK similar to racemic baclofen
  - $t_{½}$ = 5 hours




- Racemic baclofen used for spasticity
  - Approved for ages 12 and up
  - Used very frequently in younger patients with CP
  - Safety is well-established

# Seaside Therapeutics P2 study of STX209 in FXS

- Children & adults with FXS full mutation, n=63
- DB, PC, XO trial – 4 week treatment periods

| | STX209 (least squares mean ± SEM), *n* = 60* | | Placebo (least squares mean ± SEM), *n* = 62* | | *P* |
|---|---|---|---|---|---|
| | **Baseline** | **End of treatment** | **Baseline** | **End of treatment** | |
| Prespecified analyses | | | | | |
| ABC-I | 21.0 ± 1.14 | 16.4 ± 0.95 | 21.8 ± 1.29 | 16.2 ± 0.95 | 0.89 |
| CGI-I | — | 3.1 ± 0.16 | — | 3.5 ± 0.16 | 0.15 |
| CGI-S | 5.1 ± 0.13 | 4.5 ± 0.12 | 5.1 ± 0.14 | 4.8 ± 0.12 | 0.09 |
| Blinded treatment preference (clinician) | — | 26 (57%) | — | 13 (28%) | 0.05 |
| Blinded treatment preference (parent) | — | 27 (59%) | — | 15 (33%) | 0.09 |
| VAS problem behaviors | 2.2 ± 0.22 | 4.2 ± 0.32 | 1.9 ± 0.20 | 3.1 ± 0.33 | 0.04 |

*Numbers reflect *n* for analysis of ABC-I. *n* differs slightly for other variables because of missing data.

Berry-Kravis et al., 2012

# Study 22001: ABC-FXS Social Avoidance subscale

- ABC originally validated in MR/ID population
  - 58 items; 5 factors, including ABC-Lethargy/Social Withdrawal
- Validation study in FXS population (Sansone, et al., 2012)
  - 630 FXS subjects across 6 centers
  - New, validated factor score in FXS: ABC-FXS Social Avoidance

| | STX209 (least squares mean ± SEM), *n* = 60* | | Placebo (least squares mean ± SEM), *n* = 62* | | *P* |
|---|---|---|---|---|---|
| | **Baseline** | **End of treatment** | **Baseline** | **End of treatment** | |
| Prespecified analyses | | | | | |
| ABC-I | 21.0 ± 1.14 | 16.4 ± 0.95 | 21.8 ± 1.29 | 16.2 ± 0.95 | 0.89 |
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| VAS problem behaviors | 2.2 ± 0.22 | 4.2 ± 0.32 | 1.9 ± 0.20 | 3.1 ± 0.33 | 0.04 |
| Post hoc analysis | | | | | |
| ABC—Social Avoidance | 4.5 ± 0.46 | 3.3 ± 0.44 | 3.9 ± 0.43 | 3.6 ± 0.41 | 0.008 |

*Numbers reflect *n* for analysis of ABC-I. *n* differs slightly for other variables because of missing data.



Berry-Kravis et al., 2012

# Study 22001: Lower sociability subgroup

**Table 3.** Efficacy analyses in subjects with ABC-LSW ≥8 at baseline.

| | STX209 (least squares mean ± SEM), *n* = 27 | | Placebo (least squares mean ± SEM), *n* = 27 | | *P* |
|---|---|---|---|---|---|
| | **Baseline** | **End of treatment** | **Baseline** | **End of treatment** | |
| ABC-LSW | 16.2 ± 1.21 | 12.4 ± 1.43 | 16.0 ± 1.30 | 15.9 ± 1.45 | 0.07 |
| ABC—Social Avoidance | 6.8 ± 0.60 | 4.6 ± 0.54 | 5.9 ± 0.62 | 6.4 ± 0.53 | 0.04 |
| Vineland-Socialization raw score* | 80.1 ± 8.10 | 99.6 ± 3.38 | 83.1 ± 8.65 | 87.8 ± 3.19 | 0.03 |
| CGI-I | — | 2.5 ± 0.24 | — | 3.6 ± 0.25 | 0.02 |
| CGI-S | 5.4 ± 0.22 | 4.4 ± 0.21 | 5.3 ± 0.22 | 5.2 ± 0.22 | 0.009 |
| Blinded treatment preference (clinician)† | — | 16/20 (80%) | — | 4/20 (20%) | 0.01 |
| Blinded treatment preference (parent)† | — | 16/20 (80%) | — | 4/20 (20%) | 0.01 |
| Responders‡ | — | 10/21 (47.6%) | — | 2/23 (8.7%) | 0.04 |

*Vineland-Socialization raw score only had data at the end of treatment and baseline; there were no data in the middle of period. †This table reports on a subgroup of 27 subjects; only 20 subjects had data on these particular variables. Thus, seven subjects had missing data on these variables. ‡Responders were defined by a rating of "very much" or "much improved" on the CGI-I and improvement of at least 25% on the ABC-LSW. Not all 27 subjects had ABC-LSW raw score and CGI-I at the end of each treatment.

Berry-Kravis et al., 2012

# Study 22001: Safety

| | STX209 | Placebo |
|---|---|---|
| Serious Adverse Events | 1 | 0 |
| AEs leading to discontinuation | 1 | 2 |

| **Adverse event** | **STX209, *n* (%)** | **Placebo, *n* (%)** |
|---|---|---|
| Upper respiratory tract infection | 8 (13) | 6 (10) |
| Headache | 5 (8) | 1 (2) |
| Sedation | 5 (8) | 1 (2) |
| Fatigue | 4 (6) | 1 (2) |
| Irritability | 4 (6) | 4 (6) |
| Diarrhea | 3 (5) | 5 (8) |
| Increased appetite | 4 (6) | 2 (3) |
| Vomiting | 4 (6) | 1 (2) |
| Aggression | 3 (5) | 4 (6) |
| Nasopharyngitis | 2 (3) | 6 (10) |



Berry-Kravis et al., 2012

# Targeted drug development for FXS: Current status

- Potential efficacy signals found
  - mGluR5 antagonists: Aberrant behaviors, especially stereotypies
  - GABA-B agonist: Social impairments
- Larger, Phase 3 studies underway
  - AFQ056 (mavoglurant)
  - RO4917523
  - STX209 (arbaclofen)

# Targeted treatment research in other conditions

| Condition | Animal model / Drug target | Drug / Effect in animal | Human trial |
|---|---|---|---|
| NF | *Nf1* mouse / increased RAS/ERK signaling | Statins / improved attention and spatial cognition | Possible improvement in spatial skills |
| Rett syndrome | *Mecp2* mouse / reduced BDNF signaling | IGF-1 fragment / rescue of lethality, neuropathology, autonomic abnormalities | Recruiting |
| Down syndrome | Ts65Dn mouse / excessive inhibitory neurotransmission | GABA-A negative modulators / improved cognition | Recruiting |
| Tuberous sclerosis (TSC2) | TSC2 mouse / elevated mTOR signaling | Rapamycin / improved spatial learning & contextual discrimination | Recruiting |

# Relevance of FXS to ASD

- FXS accounts for 2-4% (?) of autism
  - But, feels different from non-FXS ASD
- Centrality of synaptic pathophysiology to ASD
  - FMRP regulates synaptic processes
  - Other single gene disorders
  - Genetic research

Neuron
Article

Cell PRESS

## De Novo Gene Disruptions in Children on the Autistic Spectrum

Ivan Iossifov,[1,6] Michael Ronemus,[1,6] Dan Levy,[1] Zihua Wang,[1] Inessa Hakker,[1] Julie Rosenbaum,[1] Boris Yamrom,[1] Yoon-ha Lee,[1] Giuseppe Narzisi,[1] Anthony Leotta,[1] Jude Kendall,[1] Ewa Grabowska,[1] Beicong Ma,[1] Steven Marks,[1] Linda Rodgers,[1] Asya Stepansky,[1] Jennifer Troge,[1] Peter Andrews,[1] Mitchell Bekritsky,[1] Kith Pradhan,[1] Elena Ghiban,[1] Melissa Kramer,[1] Jennifer Parla,[1] Ryan Demeter,[2] Lucinda L. Fulton,[2] Robert S. Fulton,[2] Vincent J. Magrini,[2] Kenny Ye,[3] Jennifer C. Darnell,[4] Robert B. Darnell,[4,5] Elaine R. Mardis,[2] Richard K. Wilson,[2] Michael C. Schatz,[1] W. Richard McCombie,[1] and Michael Wigler[1,*]

~50% of disrupted genes are FMRP targets

## FMRP Stalls Ribosomal Translocation on mRNAs Linked to Synaptic Function and Autism

Cell

Jennifer C. Darnell,[1,*] Sarah J. Van Driesche,[1] Chaolin Zhang,[1] Ka Ying Sharon Hung,[1] Aldo Mele,[1] Claire E. Fraser,[1] Elizabeth F. Stone,[1] Cynthia Chen,[1] John J. Fak,[1] Sung Wook Chi,[1,4] Donny D. Licatalosi,[1,5] Joel D. Richter,[3] and Robert B. Darnell[1,2,*]

ARTICLE

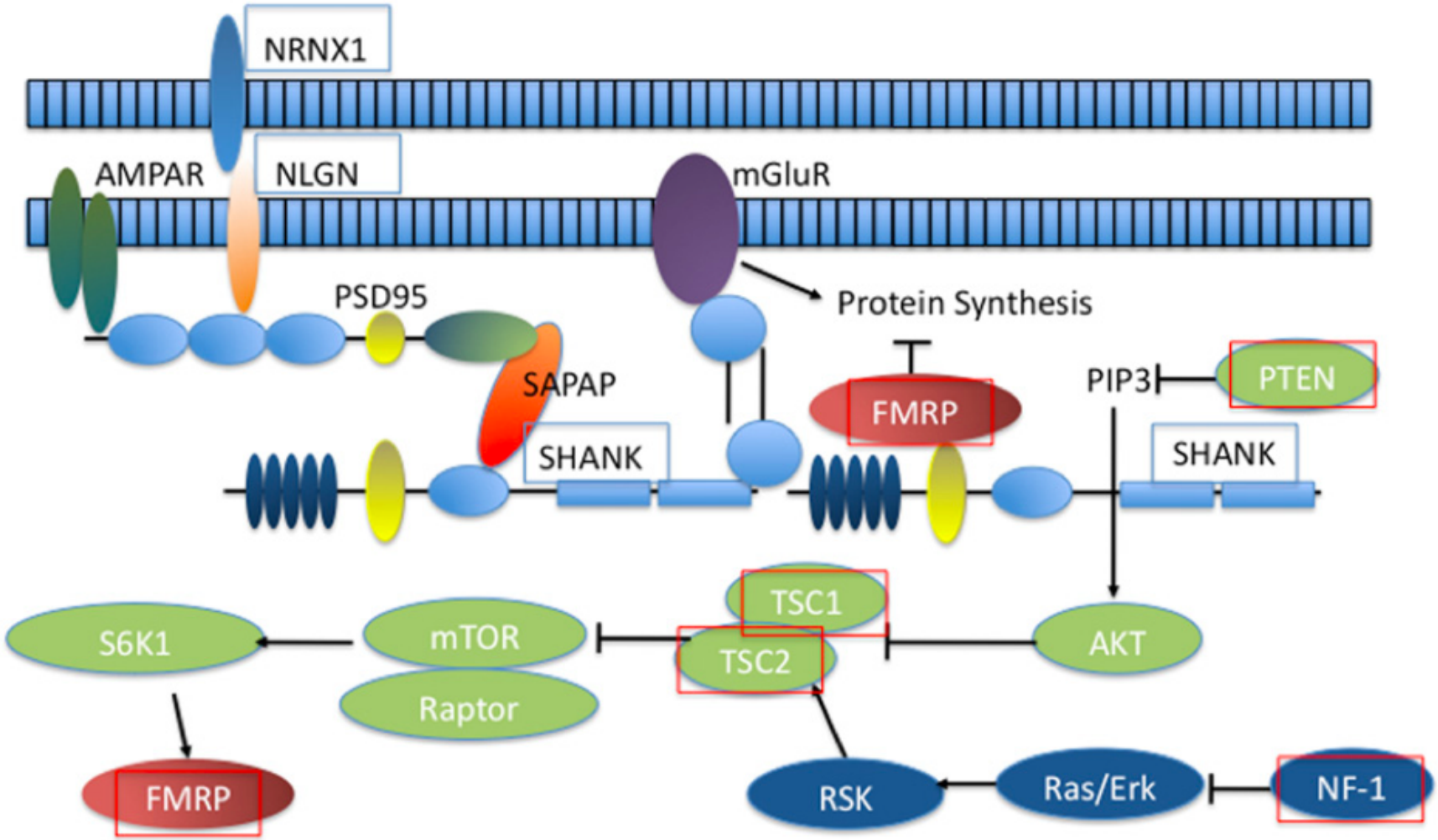
doi:10.1038/nature11737

## FMRP targets distinct mRNA sequence elements to regulate protein expression

Manuel Ascano Jr[1], Neelanjan Mukherjee[2]†, Pradeep Bandaru[1], Jason B. Miller[1], Jeffrey D. Nusbaum[1], David L. Corcoran[2], Christine Langlois[3], Mathias Munschauer[1], Scott Dewell[1], Markus Hafner[1], Zev Williams[1,3], Uwe Ohler[2]† & Thomas Tuschl[1]

FMRP regulates >90 genes independently implicated in autism

# A common signaling pathway




State, 2010

# Activity-dependent neuronal signalling and autism spectrum disorder.

Daniel H DH Ebert and Michael E ME Greenberg
Nature **493**(7432):327-37 (2013), PMID 23325215

Neuronal activity induces the post-translational modification of synaptic molecules, promotes localized protein synthesis within dendrites and activates gene transcription, thereby regulating synaptic function and allowing neuronal circuits to respond dynamically to experience. Evidence indicates that many of the genes that are mutated in autism spectrum disorder are crucial components of the activity-dependent signalling networks that regulate synapse development and plasticity. Dysregulation of activity-dependent signalling pathways in neurons may, therefore, have a key role in the aetiology of autism spectrum disorder.

DOI: 10.1038/nature11860

# Rare genetic disorder to broad population: Really ???

| | FH | Elevated cholesterol | FX | ASD |
|---|---|---|---|---|
| Prevalence | 1:1,000,000 | Not rare | 1:4,000 | Not rare |
| Genetic basis | LDLR mutation | Not LDLR<br>Not HMGCR | FMR1 triplet expansion | Not FMR1<br>Not mGluR5 |
| Core symptoms | High cholesterol | same | ASD | same |
| Relevant pathway | CHOL synthesis in liver | same | Protein synthesis at synapse | ? |
| Pharmacologic target | HMGCR | same | mGluR5 | ? |
| Drug | Statins | same | mGluR5 antag | ? |
| Drug effect | Reduced CHOL levels | same | ? | ? |

# A challenge for pediatric drug development

| | Yes | No | Not Sure |
|---|---|---|---|
| Are studies involving children necessary to advance the treatment of children? | 67% | 4% | 29% |
| Would you allow a child of yours to participate? | 25% | 30% | 45% |

Harris Poll, 2004, n=5,822